

ORIGINAL ARTICLE

Reference frame for home pulse pressure based on cardiovascular risk in 6470 subjects from 5 populations

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The absence of an outcome-driven reference frame for self-measured pulse pressure (PP) limits its clinical applicability. In an attempt to derive an operational threshold for self-measured PP, we analyzed 6470 participants (mean age 59.3 years; 56.9% women; 22.5% on antihypertensive treatment) from 5 general population cohorts included in the International Database on HOme blood pressure in relation to Cardiovascular Outcome. During 8.3 years of follow-up (median), 294 cardiovascular deaths, 393 strokes and 336 cardiac events occurred. In 3285 younger subjects (<60 years), home PP only predicted all-cause and cardiovascular mortality ($P \leq 0.036$), whereas in 3185 older subjects (≥ 60 years) PP predicted total and cardiovascular mortality ($P \leq 0.0067$) and all cardiovascular and coronary events ($P \leq 0.044$). However, PP did not substantially refine risk prediction based on classical risk factors including mean blood pressure (generalized R^2 statistic $\leq 0.20\%$). In older subjects, the adjusted hazard ratios expressing the risk in the upper decile of home PP (≥ 76 mm Hg) versus the average risk in whole population were 1.41 (95% confidence interval, 1.09–1.81; $P = 0.0081$) for all-cause mortality, 1.62 (1.11–2.35; $P = 0.012$) for cardiovascular mortality and 1.31 (1.00–1.70; $P = 0.047$) for all fatal and nonfatal cardiovascular end points combined. The low number of events precluded an analysis by tenths of the PP distribution in younger participants. In conclusion, a home PP of ≥ 76 mm Hg predicted cardiovascular outcomes in the elderly with the exception of stroke, whereas in younger subjects no threshold could be established.

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Keywords: cardiovascular diseases; epidemiology; home blood pressure; pulse pressure; thresholds

INTRODUCTION

Pulse pressure (PP), the difference between systolic and diastolic blood pressure, depends on left ventricular ejection, the elasticity of the central arteries, and the timing and intensity of the backward wave originating at reflection sites in the peripheral circulation. PP widens in the elderly, because with advancing age systolic blood pressure continues to rise, whereas the age-related increase in diastolic blood pressure levels off or even reverses in the fifth decade of life.¹ Several

studies showed that PP, derived from the conventionally measured blood pressure, predicts adverse outcomes in patients with cardiovascular² or renal disease^{3,4} as well as in populations.^{5–9} Compared with the conventionally measured blood pressure, self-measurement of blood pressure refines risk stratification.¹⁰ To our knowledge, only one population study examined the risk of stroke associated with the self-measured PP in Japanese.¹¹ Moreover, current guidelines for the management of blood pressure do not propose

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outcome-driven thresholds for PP.^{12,13} We therefore assessed the predictive value of the self-measured home PP in 6470 people randomly recruited from 5 populations and enrolled in the International Database of Home blood pressure in relation to Cardiovascular Outcome (IDHOCO).

METHODS

Study population

The construction of the IDHOCO database has been described previously.¹⁴ At the time of writing this report, we collected data from 7 prospective population studies (8912 subjects). All studies received ethical approval. For the present analysis we discarded two cohorts, because data on cause-specific mortality were still being collected,¹⁵ or because the study included patients instead of a general population sample.¹⁶ Of the 6753 remaining participants, we excluded 283 because <2 home blood pressure readings ($n=18$) or <2 conventional blood pressure readings ($n=267$) were available. Therefore, the number of participants analyzed totaled 6470, comprising 2520 inhabitants of Ohasama, Japan;¹⁷ 2075 Finns representing a nationwide sample;¹⁸ 811 inhabitants of the Tsurugaya district, Sendai, Japan;¹⁹ 399 inhabitants of Montevideo, Uruguay²⁰ and 665 inhabitants of Didima, Greece.²¹ We categorized participants into Whites (inhabitants of Finland, Didima and Montevideo) and Asians (inhabitants of Sendai and Ohasama).

Blood pressure measurement

Clinic blood pressure was measured with a standard mercury sphygmomanometer or an automated device (Elquest USM-700F (Elquest Corporation, Chiba, Japan), Omron HEM-705CP or Omron Form ABI/PWV (Omron Healthcare Co., Ltd, Kyoto, Japan)), using the appropriate cuff size. The average of the first two office blood pressure readings was used for analysis.

Participants recorded their home blood pressure after 2–5 min of rest in the sitting position with validated oscillometric devices (Omron HEM-401C, Omron HEM-722C, Omron HEM-747, Omron HEM-705CP or SpaceLabs 90207, Spacelabs Healthcare, Snoqualmie, WA, USA), using the appropriate cuff size. The median number of home blood pressure measurements ranged from 2 in Montevideo²⁰ to 52 in Ohasama.¹⁷ The mean of all available measurements was used for analysis. Home PP was systolic minus diastolic blood pressure. Mean arterial pressure was diastolic blood pressure plus one third of PP. Hypertension was a home blood pressure of at least 135 mm Hg systolic or 85 mm Hg diastolic¹³ or use of antihypertensive drugs.

Other measurements

We used the baseline questionnaires originally administered in each cohort to obtain information on each participant's medical history, intake of medications and smoking and drinking habits. Subjects using any amount of tobacco or alcohol in the period of the baseline examination were classified as smokers or drinkers. Body mass index was body weight in kilograms divided by height in meters squared. Previous cardiovascular disease included cardiac and cerebrovascular disorders and peripheral vascular disease. Serum cholesterol and blood glucose were determined by automated enzymatic methods on venous blood samples. Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of 7.0 mmol l^{-1} (126 mg dl^{-1}) or 11.1 mmol l^{-1} (200 mg dl^{-1}) or higher,²² or use of antidiabetic drugs.

Ascertainment of events

We ascertained vital status and incidence of fatal and non-fatal diseases from the appropriate sources in each country, as described in detail in a previous publication.¹⁸ Fatal and non-fatal stroke did not include transient ischemic attacks. Coronary events encompassed death because of ischemic heart disease, sudden death, non-fatal myocardial infarction, and surgical and percutaneous coronary revascularization. Cardiac events comprised coronary end points, fatal and non-fatal heart failure, pacemaker implantation and other cardiac deaths. The composite cardiovascular end point included cardiovascular mortality, cerebrovascular and cardiac endpoints. We summarized the ascertainment and definition of events in each of the cohorts in

Supplementary Table S1. In all outcome analyses, we only considered the first event per participant within each category.

Statistical analyses

For database management and statistical analysis, we used the SAS software, version 9.3 (SAS Institute, Cary, NC, USA). For comparison of means and proportions, we applied the large sample z test and the χ^2 statistic, respectively. Statistical significance was an α -level of <0.05 on two-sided tests. As described previously,¹⁴ we interpolated missing values of body mass index ($n=382$) and serum cholesterol ($n=133$) from the regression slope on age after stratification for cohort and sex. In subjects with unknown smoking habits ($n=19$) and drinking status ($n=1216$), we set the design variable to the cohort- and sex-specific mean of the codes (0,1). In the Didima cohort ($n=665$), we extrapolated cholesterol values and drinking habits by sex and age, from data provided by large population cohorts living in a similar geographical area.^{23,24}

We used Cox regression to compute hazard ratios (HRs). We checked the proportional hazards assumption and the functional forms of the covariables by the Kolmogorov-type supremum test, as implemented in the PROC PHREG procedure of the SAS software. Because the role of PP changes with age, we stratified all analyses by age 60.²⁵ To compute HRs in tenths of the PP distribution, we applied the deviation from mean coding.²⁶ This approach expresses the risk in each tenth relative to the overall risk in the whole study population and allows computing 95% confidence intervals (CIs) for the HRs in all tenths without definition of an arbitrary reference group. The HRs for PP and mean arterial pressure analyzed as continuous variables were standardized and express the risk associated with a 1-s.d. increase in the independent variable. We tested heterogeneity in the HRs across subgroups by introducing the appropriate interaction term in the Cox model. The improvement in prediction performance gained by adding PP to a model already including the conventional risk factors was assessed by the net reclassification improvement,²⁷ the integrated discrimination improvement²⁷ and Harrell's c -statistic.²⁸ We applied the generalized R^2 statistic to assess the risks additionally explained by PP over and beyond mean arterial pressure and other covariables.²⁹ We stratified Cox models for cohort and adjusted HRs for baseline characteristics including sex, age, body mass index, current smoking, alcohol intake, serum cholesterol, history of cardiovascular disease, diabetes mellitus, antihypertensive treatment, home pulse rate and mean blood pressure.

RESULTS

Characteristics of participants

The whole study population comprised 3139 Europeans (48.5%) and 3331 Asians (51.5%). Of the 6470 participants, 3680 were women (56.9%), 2786 (43.1%) had hypertension on home blood pressure measurement and 1452 (22.4%) were taking blood pressure-lowering drugs. Mean (\pm s.d.) age was 59.3 ± 13.5 years. In the whole study population, home blood pressure averaged 127.2 ± 18.2 mm Hg systolic, 76.1 ± 10.0 mm Hg diastolic, 51.1 ± 12.9 mm Hg for PP and 93.1 ± 11.9 mm Hg for mean arterial pressure. At enrollment, 1352 participants (20.9%) were current smokers and 2721 (51.8%) reported intake of alcohol. Table 1 shows the characteristics of the participants by age group and sex.

Analysis of younger participants

Incidence of end points. Among 3285 younger subjects, median follow-up was 8.3 years (5th–95th percentile interval, 7.2–16.8 years). Over 32 671 person-years of follow-up, 149 participants died (4.6 per 1000 person-years) and 161 experienced a fatal or non-fatal cardiovascular complication (5.0 per 1000 person-years). The cause of death was cardiovascular in 41 participants, non-cardiovascular in 105 and renal failure in 3. Considering cause-specific first cardiovascular events, 73 subjects experienced a fatal or non-fatal stroke (14 and 59, respectively) and 90 subjects had a fatal or non-fatal cardiac event (22 and 68).

Table 1 Baseline characteristics of participants by age group

Characteristic	< 60 years	≥ 60 years
Number of subjects (%)	3285	3185
Women	1871 (56.9)	1809 (56.8)
Asian	1225 (37.3)	2106 (66.1)
Smokers	873 (26.6)	479 (15.1)
Drinking alcohol	1540 (58.8)	1181 (44.8)
Hypertension	882 (26.9)	1904 (59.8)
On antihypertensive treatment	389 (11.9)	1063 (33.4)
Diabetes mellitus	170 (5.2)	376 (11.8)
Cardiovascular disorders	125 (3.8)	539 (16.9)
Mean (±s.d.) characteristic		
Age, years	48.3 (8.6)	70.5 (6.7)
Body mass index, kg m ⁻²	25.7 (4.2)	25.2 (4.3)
Conventional blood pressure, mm Hg		
Systolic	127.5 (18.4)	140.6 (20.3)
Diastolic	78.8 (11.9)	79.3 (11.6)
Pulse pressure	48.7 (12.9)	61.3 (15.1)
Mean arterial pressure	95.0 (13.1)	99.7 (13.3)
Self-recorded pressure		
Systolic	120.1 (15.7)	134.5 (17.8)
Diastolic	75.2 (10.4)	77.1 (9.5)
Pulse pressure	44.9 (8.9)	57.4 (13.4)
Mean arterial pressure	90.1 (11.7)	96.2 (11.2)
Self-recorded pulse rate, beats min ⁻¹	70.7 (9.0)	67.5 (8.9)
Serum cholesterol, mmol l ⁻¹	5.57 (1.1)	5.42 (1.1)

Hypertension was a home blood pressure of at least 135 mm Hg systolic or 85 mm Hg diastolic or use of antihypertensive drugs. Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of 7.0 mmol l⁻¹ (126 mg dl⁻¹) or 11.1 mmol l⁻¹ (200 mg dl⁻¹) or higher, or use of antidiabetic drugs. All differences between age groups were significant ($P<0.0001$) with the exception of conventional diastolic blood pressure ($P=0.10$) and the proportion of women ($P=0.90$).

Risk associated with home PP. The association between outcome and PP did not deviate significantly from log linearity ($P\geq 0.092$). Table 2 shows the standardized HRs associated with home mean blood pressure and home PP. With adjustments applied for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, home pulse rate, history of cardiovascular disease, diabetes mellitus and antihypertensive treatment, the home PP significantly predicted all outcomes, except fatal and non-fatal stroke. After further adjustment for mean arterial pressure, PP only predicted total mortality (HR, 1.24; 95% CI, 1.01–1.51; $P=0.036$) and cardiovascular deaths (HR, 1.47; CI, 1.03–2.10; $P=0.033$). The results of a similar analysis on the association between outcome and home PP adjusted for home systolic blood pressure are shown in Supplementary Table S2. The small number of events precluded an analysis by tenths of the home PP distribution in younger participants.

Analysis of older participants

Incidence of end points. Among 3185 older subjects, median follow-up was 8.2 years (5th–95th percentile interval, 7.2–16.8 years). Over 26 655 person-years of follow-up, 663 participants died (24.9 per 1000 person-years) and 555 experienced a fatal or non-fatal cardiovascular complication (22.0 per 1000 person-years). The cause of death was cardiovascular in 253 participants, non-cardiovascular in 395, renal failure in 10 and unknown in 5. Considering cause-specific first cardiovascular events, 320 subjects experienced a fatal or non-fatal stroke (64 and 256, respectively) and 246 subjects had a fatal or non-fatal cardiac event (127 and 119).

Risk associated with home PP. In older subjects (age ≥ 60 years), the association between outcome and PP did not deviate significantly from log linearity ($P\geq 0.15$). Considering fully adjusted models, the home PP predicted all of the end points ($P\leq 0.044$), except fatal combined with non-fatal cardiac events ($P=0.052$) and stroke

Table 2 Standardized hazard ratios relating outcomes to home pulse pressure and mean arterial pressure by age group

		Age < 60 years			Age ≥ 60 years		
		Hazard ratios			Hazard ratios		
End point	Model	N° events	Mean pressure	Pulse pressure	N° events	Mean pressure	Pulse pressure
Mortality							
All causes	A	149	1.24 (1.01–1.51)*	1.28 (1.08–1.52)†	663	1.04 (0.95–1.13)	1.14 (1.05–1.25)‡
	FA		1.08 (0.86–1.37)	1.24 (1.01–1.51)*		0.96 (0.86–1.06)	1.17 (1.06–1.30)‡
	A	41	1.44 (0.98–2.10)	1.56 (1.15–2.11)‡	253	1.08 (0.94–1.24)	1.22 (1.07–1.40)‡
	FA		1.15 (0.75–1.77)	1.47 (1.03–2.10)*		0.96 (0.82–1.14)	1.25 (1.06–1.47)‡
Fatal plus non-fatal events							
All cardiovascular	A	161	1.50 (1.24–1.80)§	1.34 (1.15–1.56)§	555	1.26 (1.15–1.38)§	1.25 (1.14–1.36)§
	FA		1.35 (1.09–1.68)†	1.18 (0.98–1.41)		1.18 (1.06–1.32)†	1.14 (1.02–1.27)*
Cardiac	A	90	1.66 (1.31–2.10)§	1.38 (1.15–1.66)‡	246	1.01 (0.88–1.16)	1.12 (0.98–1.27)
	FA		1.50 (1.12–2.00)†	1.15 (0.92–1.45)		0.91 (0.77–1.09)	1.18 (1.00–1.39)
Coronary	A	76	1.54 (1.20–2.00)‡	1.26 (1.03–1.55)*	175	1.03 (0.87–1.21)	1.15 (0.99–1.34)
	FA		1.49 (1.08–2.06)*	1.05 (0.81–1.35)		0.90 (0.73–1.11)	1.22 (1.00–1.49)*
Stroke	A	73	1.25 (0.94–1.68)	1.31 (1.01–1.71)*	320	1.51 (1.34–1.70)§	1.37 (1.21–1.56)§
	FA		1.13 (0.82–1.56)	1.25 (0.94–1.68)		1.42 (1.23–1.63)§	1.14 (0.98–1.32)

Hazard ratios, presented with 95% confidence interval, express the risk associated with a 1-s.d. (11.7 mm Hg and 11.2 mm Hg in subjects <60 years and ≥ 60 years, respectively) increase in mean home blood pressure or a 1-s.d. (8.8 mm Hg and 13.4 mm Hg) increase in home pulse pressure. All models were stratified for cohort and adjusted for sex, age, body mass index, smoking and drinking, serum cholesterol, home pulse rate, diabetes mellitus, history of cardiovascular disease, and antihypertensive treatment. Adjusted models (A) include either the mean blood pressure or pulse pressure, while fully adjusted models (FA) include both mean blood pressure and pulse pressure in addition to the aforementioned covariates. Significance of the hazard ratios: * $P<0.05$, † $P<0.01$, ‡ $P<0.001$, and § $P<0.0001$.

($P=0.083$; Table 2). Supplementary Table S2 shows the results of a similar analysis using systolic blood pressure instead of mean blood pressure. The generalized R^2 statistics for adding home PP as a predictor of outcome over and beyond mean arterial pressure was

0.20% for cardiovascular mortality and 0.14% for fatal combined with non-fatal cardiovascular events (Table 3).

Figure 1 shows the multivariable-adjusted HRs comparing the risk in tenths of the distribution of home PP versus the average risk in all

Table 3 Predictive value of the Cox regression models in participants aged 60 or more

Models	Cardiovascular mortality						Cardiovascular events					
	Likelihood ratio	P-value	R^2 (%)	NRI (%)	IDI (%)	C (%)	Likelihood ratio	P-value	R^2 (%)	NRI (%)	IDI (%)	C (%)
Basic model	332.3	...	9.91	52.2	327.2	...	9.80
Mean home blood pressure added to basic model	1.2	0.27	0.03	1.11	-0.20	0.04	24.8	<0.0001	0.70	17.6	5.6	0.92
Systolic home pressure added to basic model	4.6	0.031	0.13	6.70	0.05	0.35	29.7	<0.0001	0.84	21.9	7.6	1.22
Home pulse pressure added to basic model	8.2	0.0042	0.23	7.81	1.50	0.74	21.2	<0.0001	0.60	11.1	5.9	0.96
Home pulse pressure added to basic model also including mean blood pressure	7.2	0.0074	0.20	13.4	2.50	0.74	5.0	0.026	0.14	4.3	1.8	0.31
Home pulse pressure added to basic model also including systolic blood pressure	3.7	0.053	0.11	6.31	2.25	0.44	0.00	0.96	0.00	5.9	-0.0	0.00

The basic model included cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, home pulse rate, diabetes mellitus, history of cardiovascular disease and antihypertensive treatment. P -values are for the improvement of the fit across nested models. Values are likelihood ratios, generalized R^2 -statistics, net reclassification improvement (NRI), relative integrated discrimination improvement (IDI) and the improvements in Harrell's C statistic (C) by adding mean home blood pressure, home systolic blood pressure or home pulse pressure to the reference model.

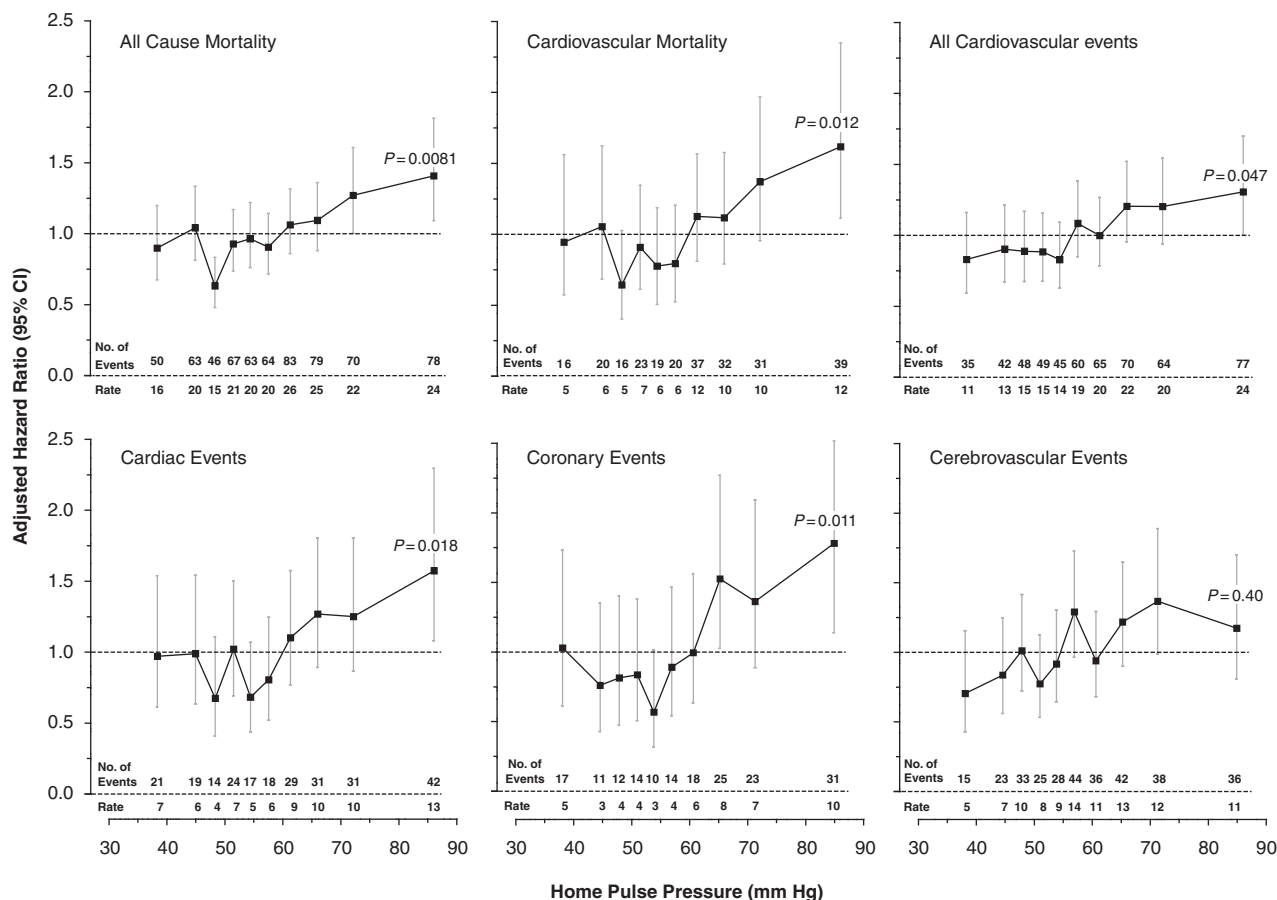


Figure 1 Multivariable-adjusted hazard ratios (95% confidence intervals) by tenths of the home pulse pressure distribution in 3185 older subjects (≥60 years). The hazard ratios express the risk in tenths of the distribution compared with the average risk in all elderly and were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, home pulse rate, home mean blood pressure, diabetes mellitus, history of cardiovascular disease and antihypertensive treatment. The number of events and incidence rates (in percent) are also given for each tenth. P -values are provided for the hazard ratio in the top tenth.

Table 4 Standardized hazard ratios for cardiovascular mortality and cardiovascular events in older participants in relation to home pulse pressure in different strata

Subgroup	At risk (n)	Events (n)	Hazard ratio (CI)	P-value
<i>Cardiovascular mortality</i>				
All participants	3185	253	1.25 (1.06–1.45)	0.0067
Women	1809	114	1.10 (0.85–1.43)	0.46
Men	1376	139	1.43 (1.15–1.77)	0.0014
Hypertension	1904	186	1.30 (1.08–1.55)	0.0045
Normotension	1281	67	1.04 (0.62–1.73)	0.89
Treated	1063	125	1.21 (0.96–1.52)	0.11
Untreated	2114	127	1.27 (1.01–1.60)	0.044
Whites	1079	74	1.04 (0.76–1.41)	0.82
Asians	2106	179	1.37 (1.12–1.68)	0.0022
<i>Fatal and non-fatal cardiovascular events</i>				
All participants	3185	555	1.14 (1.02–1.27)	0.025
Women	1809	252	1.03 (0.87–1.23)	0.71
Men	1376	303	1.23 (1.06–1.42)	0.0069
Hypertension	1904	410	1.15 (1.01–1.30)	0.032
Normotension	1281	145	1.24 (0.89–1.74)	0.21
Treated	1063	262	1.08 (0.92–1.27)	0.33
Untreated	2114	291	1.17 (1.00–1.36)	0.057
Whites	1079	197	1.01 (0.83–1.22)	0.91
Asians	2106	358	1.21 (1.05–1.40)	0.0087

Hazard ratios (95% confidence intervals (CIs) were calculated in subjects ≥ 60 years and express the risk associated with a 1-s.d. (13.1 mm Hg) increase in home pulse pressure. All models were stratified for cohort and adjusted for sex, age, body mass index, smoking and drinking, serum cholesterol, home pulse rate and mean blood pressure, diabetes mellitus, history of cardiovascular disease and antihypertensive treatment. Hazard ratios did not differ significantly between subgroups ($P > 0.19$). Whites were recruited in Didima, Finland and Montevideo and Asians in Ohasama and Sendai.

of the elderly. The HRs reached statistical significance in the ninth (1.27; CI, 1.00–1.61; $P = 0.046$) and in the upper (1.41; CI, 1.09–1.81; $P = 0.0081$) tenths for total mortality, and in the upper tenth for cardiovascular mortality (1.62; CI, 1.11–2.35; $P = 0.012$), all cardiovascular events (1.31; CI, 1.00–1.70; $P = 0.047$), all cardiac events (1.57; 1.08–2.30; $P = 0.018$) and all coronary events (1.78; CI, 1.14–2.78; $P = 0.011$). The risk of stroke in the upper tenth did not exceed the average risk among all elderly (HR, 1.17; CI, 0.81–1.70; $P = 0.40$). PP in the ninth and top tenth of the distribution of home PP averaged 71.3 mm Hg (range, 67.8–75.9 mm Hg) and 84.9 mm Hg (range, 76.0–125.8 mm Hg).

Sensitivity analyses. We checked the consistency of our results for cardiovascular mortality and for fatal and non-fatal cardiovascular events combined (Table 4), according to various baseline characteristics in older participants. The HRs expressing the risk associated with a 1-s.d. (13.1 mm Hg) increase in home PP were not statistically different between subgroups ($0.19 \leq P \leq 0.93$). In addition, our results did not materially change after excluding one cohort at a time. Finally, we repeated our analyses using tenths of the distribution of the conventionally measured PP instead of home PP. PP in the top tenth of the distribution of the conventionally measured PP averaged 90.6 mm Hg (range, 81.0–159.0 mm Hg). With adjustments applied as before, this level of conventional PP was associated with increased total mortality (HR, 1.36; CI, 1.10–1.70; $P = 0.006$), but not with excess cardiovascular mortality (HR, 1.21; CI, 0.86–1.71; $P = 0.27$), or cardiovascular (HR, 1.06; CI, 0.83–1.36; $P = 0.63$) or cardiac (HR, 1.13; CI, 0.79–1.63; $P = 0.49$) events.

DISCUSSION

To our knowledge, our current study provides the first population-based findings on the incremental value of self-measured PP in the prediction of mortality and cardiovascular events over and beyond traditional risk factors, including mean arterial pressure, the steady component of blood pressure.⁵ Below age 60, home PP predicted all-cause and cardiovascular mortality. From age 60 onwards, home PP predicted total and cardiovascular mortality and all cardiovascular and coronary events. In the elderly, a PP of ≥ 76 mm Hg was associated with adverse cardiovascular outcomes, but not including stroke. However, PP did not substantially refine risk prediction based on classical risk factors including mean arterial pressure.

The only prior outcome-based population study reporting on the predictive value of self-measured PP was the Ohasama study.^{11,30} Among 2369 subjects without a history of stroke (mean age, 59 years; 60% women), 238 strokes occurred during 11.7 years of follow-up.¹¹ In line with our current findings, PP was a weaker predictor of stroke than mean arterial pressure.¹¹ Among 1913 Ohasama participants, followed up for 8.3 years, 93 died because of cardiovascular disease.³⁰ Each 10 mm Hg increment in the home PP was associated with a higher risk of cardiovascular mortality (HR, 1.37; CI, 1.14–1.55; $P = 0.001$).³⁰ The analysis focusing on stroke was adjusted for sex, age, smoking, use of antihypertensive medication, hypercholesterolemia, diabetes mellitus and history of heart disease.¹¹ The analysis of cardiovascular mortality was adjusted for the same covariables plus obesity.³⁰ Obesity was a body mass index exceeding 25.0 kg m^{-2} , not 30 kg m^{-2} , and the overall prevalence was 20.5%, which seems to be higher than expected for Japanese. The Ohasama results are not representative for other ethnicities and were not adjusted for body mass index, home pulse rate and drinking status. However, our current study that includes 48.5% Whites and the Ohasama results^{11,30} are consistent with the concept that PP, representing the pulsatile component of blood pressure, is the dominant predictor of cardiac events,³¹ whereas mean arterial pressure, representing the steady component of blood pressure, is the dominant predictor of stroke.^{6,32}

Several longitudinal population studies^{19–21,33} attempted to establish cardiovascular prognosis and diagnostic cutoff limits for blood pressure components derived from home-based measurements. However, up to this day, they did not address outcome-driven thresholds for home PP. To our knowledge, the PARTAGE (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population) study³⁴ is the only study that reported on the 2-year predictive value of the self-measured PP in a cohort of patients. The study included 1126 very old participants (77.6% women; mean age, 88 years), who were living in French and Italian nursing homes. At baseline, participants measured their blood pressure following the ‘rule of 3’ (three measurements with intervals of 1 min in the morning and evening for 3 consecutive days). During follow-up, 247 participants died and 228 experienced a major cardiovascular event. The self-measured PP averaged 65 mm Hg, but was not a significant predictor either of total mortality (HR for +10 mm Hg, 0.90; CI, 0.81–1.00; $P = 0.057$) or of cardiovascular events (HR, 0.98; CI, 0.89–1.09; $P = 0.74$). Several cross-sectional studies in patients addressed the association between intermediate signs of target organ damage and PP. However, results obtained in patients, in particular from cross-sectional studies, are not representative of populations and are not relevant to the research question addressed in our current manuscript.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure¹²

proposed that PP is only marginally stronger than systolic blood pressure for risk stratification in individuals over age 60, and that under age 60, PP is not predictive. The 2007 European guideline³⁵ stated that PP is a derived measure, which combines the imprecision of the original systolic and diastolic measurements and that, although levels of 50–55 mm Hg have been suggested, no practical cutoff values separating PP normality from abnormality were available. The 2013 European guideline¹³ increased this threshold to 60 mm Hg without any justification. Our current analyses established that below age 60, total and cardiovascular mortality were log linearly associated with home PP, but that due to the small number of events no outcome-driven threshold could be established. In the elderly, home PP predicted all end points with the exception of stroke, but the refinement of prognostication over and beyond traditional risk factors and the steady component of blood pressure was small. Among elderly, the threshold delineating increased risk of death is around 68 mm Hg and for fatal combined with non-fatal cardiovascular events 76 mm Hg. Using the same approach for conventional PP in elderly participants identified a threshold of around 91 mm Hg for an increased risk of cardiovascular complications.

The current sensitivity analysis showed that home PP was a significant predictor of cardiovascular mortality and cardiovascular events in Asians but not in Whites. However, the HRs were not significantly different between the two races (Table 4) indicating that this finding might be due to chance.

The strong points of our current report are the relatively large sample size and the large number of events, which occurred over a median follow-up of >8 years. However, our current results must also be interpreted within the context of their potential limitations. First, the anthropometric characteristics and the time of recruitment within the IDHOCO database differed between cohorts, and clinic and home BP measurements were not standardized in terms of device type, number of measurements and intervals between readings. Second, our analysis rested on five population-based cohorts with an overrepresentation of Asians and Caucasians, and might not be representative for other ethnic groups, in particular Blacks. Third, for a limited number of covariables, we used interpolated data. However, sensitivity analyses from which we excluded the Didima cohort were confirmatory. Finally, the generalized R^2 is not a perfect measure of the variation explained by Cox models. Nevertheless, a measure of explained variance is essential for the correct interpretation of the prognostic value of a risk factor, because P -values of HRs do not necessarily reflect clinical significance.

In conclusion, home PP adds little information on cardiovascular outcomes below age 60 based on our observations in randomly recruited people. In the elderly, home PP is a weak risk factor with levels below 68 mm Hg probably being innocuous. However, using this threshold in clinical practice might be of little value, because home PP does not substantially enhance risk stratification over and beyond the steady component of the blood pressure level and other cardiovascular risk factors. Our current findings might inform future guidelines and lead to a consensus about a threshold for PP that is justified by health outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (<http://www.nature.com/hr>)

Hypertension Research

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed.
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Supplement to: Reference Frame for Home Pulse Pressure Based on Cardiovascular Risk in 6470 Subjects from 5 Populations. *Hypertension Research* 2013; published online.
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Table S1. Ascertainment of Events and International Classification of Diseases Codes (10th edition) applied in each cohort

	Ohasama	Finn-Home	Tsurugaya	Didima	Montevideo
Ascertainment of events					
Fatal	Death certificates	Death certificates	NHI database Medical records	Death certificates	Death certificates
Non-fatal	Stroke registration system Medical records	Hospital discharge register	NHI database Medical records	Interviews Medical records	Interviews Medical records
ICD-10 codes, if available					
Stroke	I60–I64	I61, I63	I60-I64	Investigator-defined	Investigator-defined
Sudden death	I46, R96	I46, R96	I46, R96	Investigator-defined	Investigator-defined
Heart failure	I50, J81	I50	I50	Investigator-defined	Investigator-defined
Peripheral arterial disease	I70–I74	I70-I74	I70-I74	Investigator-defined	Investigator-defined
Ischemic heart disease	I21–I25	I21-I25	I21-I25	Investigator-defined	Investigator-defined
Other cardiac death	I05, I11, I34, I35, I38, I44, I47–I49, I99	I11	-	Investigator-defined	Investigator-defined

ICD-10, The International Statistical Classification of Diseases, 10th revision; NHI, National Health Insurance

Table S2. Standardized Hazard Ratios Relating Outcomes to Home Pulse Pressure and Systolic Pulse Pressure by Age Group.

		Age <60 years			Age ≥60 years		
		Hazard Ratios			Hazard Ratios		
Endpoint	Model	N° Events	Systolic Pressure	Pulse Pressure	N° Events	Systolic Pressure	Pulse Pressure
Mortality							
All causes	A	149	1.30 (1.08–1.57)†	1.28 (1.08–1.52)†	663	1.09 (1.00–1.19)*	1.14 (1.05–1.25)†
	FA		1.12 (0.81–1.53)	1.19 (0.90–1.57)		0.93 (0.79–1.09)	1.22 (1.03–1.43)*
Cardiovascular	A	41	1.60 (1.12–2.29)*	1.56 (1.15–2.11)†	253	1.17 (1.02–1.34)*	1.22 (1.07–1.40)†
	FA		1.20 (0.68–2.15)	1.37 (0.83–2.26)		0.94 (0.73–1.22)	1.29 (1.00–1.66)
Fatal Plus Nonfatal Events							
All cardiovascular	A	161	1.51 (1.27–1.79)§	1.34 (1.15–1.56)§	555	1.29 (1.18–1.42)§	1.25 (1.14–1.36)§
	FA		1.49 (1.12–2.00)†	1.01 (0.78–1.30)		1.30 (1.09–1.54)†	1.00 (0.84–1.19)
Cardiac	A	90	1.61 (1.30–2.00)§	1.38 (1.15–1.66)‡	246	1.07 (0.93–1.22)	1.12 (0.98–1.27)
	FA		1.71 (1.16–2.54)†	0.94 (0.67–1.32)		0.87 (0.66–1.14)	1.27 (0.96–1.67)
Coronary	A	76	1.47 (1.16–1.85)†	1.26 (1.03–1.55)*	175	1.09 (0.93–1.27)	1.15 (0.99–1.34)
	FA		1.71 (1.11–2.63)*	0.86 (0.59–1.25)		0.85 (0.61–1.18)	1.33 (0.96–1.84)
Stroke	A	73	1.34 (1.00–1.80)*	1.31 (1.01–1.71)*	320	1.54 (1.36–1.74)§	1.37 (1.21–1.56)§
	FA		1.18 (0.77–1.81)	1.18 (0.80–1.74)		1.74 (1.39–2.17)§	0.86 (0.69–1.08)

Hazard ratios, presented with 95% confidence interval, express the risk associated with a 1-SD (15.7 mm Hg and 17.8 mm Hg in subjects <60 years and ≥60 years, respectively) increase in systolic home blood pressure or a 1-SD (8.8 mm Hg and 13.4 mm Hg) increase in home pulse pressure. All models were stratified for cohort and adjusted for sex, age, body mass index, smoking and drinking, serum cholesterol, home pulse rate, diabetes mellitus, history of cardiovascular disease, and antihypertensive treatment. Adjusted models (A) include either the mean blood pressure or pulse pressure, while fully adjusted models (FA) include both mean blood pressure and pulse pressure in addition to the aforementioned covariates. Significance of the hazard ratios: * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$, and § $P < 0.0001$.